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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
11/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/630,968	ROSSI ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,17,19-23 and 30-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,17,19-23 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on August 29, 2008.

Currently, claims 1-9, 17, 19-23, and 30-32 are under examination on the merits.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

Claims 1-9, 17, and 19-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Engelke et al. and Livache et al. for the reasons of record as set forth in the Office action mailed on March 7, 2008 and for the reasons stated below.

Applicant's arguments filed on August 29, 2008 have been fully considered but they are not persuasive. Applicant asserts that since the disclosure of Engelke et al. discusses the use of PCR to express U6 expression cassettes by citing "Castanotto and Rossi (2002) in preparation" in

paragraph 0196, it is unlikely that the provisional application of Engelke et al. provides adequate support for the use of PCR for U6-containing siRNA cassettes and therefore the Engelke et al. publication is not prior art to the claimed invention. It appears that applicant has misinterpreted the previous Office action. As clearly stated in the Office action, it was never stated or argued that Engelke et al. taught the "use of PCR to express U6 expression cassettes". Instead, the Office action states that Engelke et al. taught the use of a recombinant expression vector construct wherein a U6 promoter expresses siRNA molecules in mammalian cells. In addition to disclosing the U6 promoter-containing siRNA expression vector, it was clearly stated that Engelke et al. taught that PCR is a method for amplifying a segment of a genetic sequence without cloning or purification. See pages 3-4 of the Office action dated Mary 7, 2008. Hence, contrary to applicant's assertions, the provisional application of Engelke et al., Application No. 60/332,170 filed on November 14, 2001, provides adequate support for the content of the disclosure relied on for the currently pending 103(a) rejection. With regard to the actual utility of PCR for generating expression cassettes, the Livache et al. U.S. Patent was cited, and the claims were rejected in view of the combined teachings of Engelke et al. and Livache et al. Hence, whether or not the Engelke et al. publication cites a 2002 manuscript in preparation is irrelevant to the patentability and obviousness of the claimed invention. Again, only those pieces of disclosure of the Engelke et al. publication that have adequate support in the provisional application were used, stated, and relied on for the 103(a) rejection presented in the previous Office action. See the underlined sentence on page 4 of the previous Office action.

Applicant further alleges that nobody in the art knew that directly transfected PCR-amplified mini gene would be stable and produce a functional gene in cells. First, the alleged

"novel" step of directly transfecting PCR-amplified mini gene is not recited in claims 1-9. Second, contrary to applicant's allegation, the ability of an expression vector for expressing short-length genes is not dependent on how it is constructed (e.g., PCR-amplification or cloning), but on the promoter driving the short-length genes. For example, Engelke et al. taught that U6 snRNA promoter has been known in the art for expressing small RNA inserts such as antisense oligonucleotides, aptamers, and ribozymes. See page 36 of the provisional application and paragraph 0135 of Engelke et al. Furthermore, the fact that the small mini gene siRNA transcription depends on the promoter becomes more evident by applicant's amendment of the claims. See for example claim 1, which is now amended to recite that the promoter sequence transcribes the claimed siRNA molecule in mammalian cells.

Applicant further argues that Livache et al. do not teach PCR amplification using primers complementary to a promoter sequences and comprise the sense or the antisense strand sequence of an siRNA. Applicant is correct that Livache et al. do not teach that the primers comprise two-part sequence comprising a promoter sequence and a sense/antisense siRNA strand sequence. However, as stated previously in the prior Office action, Livache et al. taught that PCR-based amplification method is useful in producing a double-stranded RNA expression cassette structure comprising using a two-part sequence primer comprising a promoter sequence and a target sequence. In addition, Engelke et al. also taught that PCR-based amplification method can produce a desired, double-stranded nucleotide product without extraneous steps of cloning or purification, which therefore was suggested by Livache et al. to be more rapid and inexpensive compared to conventional cloning process of producing double-stranded expression cassettes. Hence, in view of the combined teachings of Engelke et al. and Livache et al., it would have

been obvious to one of ordinary skill in the art to make and use a two-part primer sequence that can simultaneously amplify both the promoter sequence and the following target sequence, which can be either the siRNA sense strand sequence or the siRNA antisense strand sequence in the instant case. Since the skills and knowledge required to arrive at the claimed invention were not only available but also within the technical grasp of one of ordinary skill in the art at the time of the invention, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing. Hence, this rejection is maintained.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

Claims 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Engelke et al. (citation of record) in view of Livache et al. (citation of record), Noonberg et al. (US 5,624,803) and Dietz (US 5,814,500).

The claims are newly entered claims, which are drawn to an amplification-based method of producing a mammalian promoter-containing siRNA cassette, wherein the mammalian promoter is a U6, H1, or U1 snRNA promoter.

Engelke et al. teach a U6 promoter-containing siRNA expression cassette further comprising a transcription termination sequence, which is constructed by molecular cloning technology and a method of transfecting the cassette into mammalian cells. See Figure 1A and paragraphs 0017-0020, 0088-0091, 0124-0126, 0140. They teach that synthesis of siRNA molecules is expensive and the naked siRNA molecules do not achieve long-term expression in the appropriate subcellular location. See paragraphs 0008, 0132. They teach that to remedy the

problems associated with the cost of synthesizing siRNA molecules and the short-term expression of such naked siRNA molecules in appropriate location of cells, one of ordinary skill in the art can make a recombinant expression vector construct wherein a U6 promoter expresses siRNA molecules in mammalian cells. See paragraphs 0008, 0132, 0134-0138. They teach that PCR is a method for amplifying a segment of a target sequence without cloning or purification, wherein the method comprises a step of introducing two oligonucleotide primers to a reaction mixture containing the desired target sequence, wherein the two oligonucleotide primers are complementary to their respective strands of the double stranded target sequence. They teach that the steps of denaturation, primer annealing, and polymerase extension can be repeated as many times as possible to obtain a high concentration of an amplified segment of the desired target sequence. See paragraphs 0073-0076. Note that all of the pertinent teachings of Engelke et al. described herein are adequately supported by the disclosure of their provisional application filed on November 14, 2001. Engelke et al. do not teach that the U6 promoter-containing siRNA expression cassette is constructed by PCR-amplification method, nor do they teach that the mammalian promoter is other than U6, such as the claimed H1 or U1 snRNA promoter.

Livache et al. teach a method of producing a double-stranded RNA expression cassette containing a promoter via a PCR-based method by integrating oligonucleotide primers that are complementary sequences that encompass the sequence of a promoter and the target sequence, wherein the duplex RNA has a defined length. They teach that such method is rapid and inexpensive.

Noonberg et al. teach an RNA polymerase III promoter-containing vector for expressing and generating short oligonucleotides such as antisense oligonucleotides and ribozymes, wherein

the RNA polymerase III promoter is a human U6 promoter or a human H1 promoter. See claims 2, 7-12.

Dietz teaches an RNA polymerase II promoter-containing vector for expressing an antisense oligonucleotide or a ribozyme, wherein the RNA polymerase II is a mammalian U1 snRNA promoter. See claims 1-2, 7-8.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cloning method of making a U6-promoter containing siRNA expression cassette for the PCR-amplified method of making a U6 or H1 or U1 snRNA promoter-containing siRNA expression cassette.

One of ordinary skill in the art would have been motivated to do so because Engelke et al. taught that PCR is a method for amplifying a segment of a target sequence without cloning or purification by utilizing two oligonucleotide primers that are complementary to their respective strands of the double stranded target sequence and because Livache et al. taught that double-stranded RNA expression cassette constructs can be made via a PCR-based amplification method by utilizing oligonucleotide primers that are complementary sequences that encompass the sequence of a promoter and the target sequence. Since an siRNA molecule-containing expression vector driven by a U6 promoter was desired in the art compared to naked siRNA molecules, which are expensive to synthesize and have a short life span in cells as taught by Engelke et al., one of ordinary skill in the art would have been motivated to try a different methodology of constructing such expression vector other than the cloning/purification methods used by Engelke et al. Since PCR was a well-known method to amplify target gene sequence as evidenced by Engelke et al. and Livache et al., and since PCR was also known to produce a double-stranded

RNA expression cassette both rapidly and inexpensively as taught by Livache et al., one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed PCR-amplification method of making an siRNA expression cassette. Furthermore, since both mammalian H1 promoter and U1 snRNA promoter were known to be useful for expression short-length oligonucleotide molecules as taught by Noonberg et al. and Dietz, one of ordinary skill in the art would have been motivated to substitute the mammalian U6 promoter of Engelke et al. for the functionally equivalent mammalian H1 promoter of Noonberg et al. or the mammalian U1 snRNA promoter of Dietz with a reasonable expectation of success. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
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